

Amendments to the Drawings:

The drawing sheet attached in connection with the above-identified application containing Figure 9 is being presented as a new formal drawing sheet or sheets to be substituted for the previously submitted drawing sheet or sheets. The drawing Figure 9 has been amended.

The specific changes which have been made to Figure 9 are that overlapping characters have been removed and the figure has been more clearly labeled.

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

In the specification, paragraphs [0006], [0019] and [0021] are amended, and a replacement Detailed Description section is presented to provide clearer identification of trademarks.

Claims 15-18 are requested to be cancelled.

Claims 1, 3 and 29 are currently being amended. Support for this amendment can be found, *inter alia*, in the Examples.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-14 and 19-36 are now pending in this application, of which claims 30-36 are withdrawn.

Drawings

The Examiner states that Figure 9 shows modified forms of construction in the same view, is not clearly labeled, and the labels are overlapping and appear to be numbers imposed with letters. Applicants submit replacement Figure 9 in which the overlapping characters have been removed and the figure is clearly labeled.

Specification

The Examiner states that trademarks should be capitalized wherever they appear and generic terminology be provided. In the present amendment Applicants have capitalized trademarks and inserted generic terminology at the first instance where they appear in the amended paragraphs and replacement Detailed Description section appended hereto.

Claim objections

The Examiner objected to claims 15-18 under 37 CFR 1.75(c), as being of improper form for failing to further limit the subject matter of the previous claim. Without acquiescing and solely to advance prosecution, Applicants have canceled claims 15-18. Therefore, withdrawal of the objection is respectfully requested.

Claim rejections 35 USC §112

The Examiner states that claims 15, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Without acquiescing and solely to advance prosecution, Applicants have canceled claims 15, 17 and 18. Therefore, withdrawal of the rejection is respectfully requested.

Claim rejections under 35 USC §103

At paragraph 8 of the detailed action the Examiner rejected the claims under 35 USC § 103(a) as unpatentable over the combinations of Cais (US Patent 4,205,952), Foster et al. (US Patent 4,444,879), Maggio (Immunoenzyme Technique I, 1980), Nielsen et al. (Spectrochimica Acta, 1998), Anbar (US Patent 4,002,876), Crooke (WO 99/451,450) and Mire-Sluis et al. (J. of Immunological Methods 1995). Applicants respectfully traverse the rejections, on the following grounds:

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, a prior art reference (or references) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Cais:

Cais discloses a method of tagging biologically active materials with elements, including transition elements. The tagged biologically active materials are complexed with ligands in a heterogeneous specific binding assay. The elements are detected in a variety of detection systems including an emission spectrophotometer. Among other features, Cais differs from the instant application in not teaching the detection and measuring of the transition element by an inductively coupled plasma mass spectrometer or inductively coupled plasma optical emission spectrometer. Applicants have amended claims 1, 3, and 29 by replacing the phrase, "using an atomic mass or optical spectrometer having a source of ions or atomic ions" with the phrase, "by an inductively coupled plasma mass spectrometer or an inductively coupled plasma emission spectrometer". Accordingly, Cais does not disclose all of the claim limitations in the amended claims.

I. Foster et al.:

The Examiner rejected claims 1-5, 10-14, 20-21 on the basis of obviousness with regard to Cais in view of Foster et al. Foster et al. discloses an immunoassay and a method of providing reagents in a kit. Foster et al. does not disclose a method of mass spectrometry or elemental analysis by an inductively coupled plasma mass spectrometer or inductively coupled plasma optical emission spectrometer. The combination of Cais and Foster et al. does not provide all the elements of the amended claims. Applicants request that the rejection be withdrawn.

II. Maggio:

The Examiner rejected to claims 6-9 on the basis of obviousness with regard to Cais in view of Foster et al. and Maggio. Maggio discloses a solid reagent immobilization immunoassay, but does not disclose ICP-MS. Accordingly, the cited references do not provide all the elements of the amended claims. Applicants request that the rejection be withdrawn.

III. Neilson:

The Examiner rejected claims 15-18 and 29 on the basis of obviousness with regard to Cais, in view of Foster and Neilson, stating that Neilson discloses laser ablation followed by analysis by ICP-MS. Claims 15-18 are canceled.

Neilson discloses a method to identify serum proteins that naturally bind metals (cobalt). There was no intention to label biological materials or analytes that do not normally bind metals, with transition elements.

Neilson employs immunoelectrophoresis to separate the proteins. Again, this is an entirely different purpose than that proposed in the present invention. The separation is accomplished first according to migration in an electric field and secondly according to diffusion gradients proportional to the affinity of the protein with an associated antibody. Therefore, the antibodies are used to provide a diffusion gradient. The antibodies are not tagged with elements to provide determination of proteins that do not contain the element. Applicants maintain that there would be no motivation to combine the references because of the use of the antibodies in Neilson is not the same nor remotely similar to the use of antibodies in the present invention. Moreover, the present invention is not limited to usage of antibodies. The elemental tag could be attached to any affinity product and/or to the antigen itself. Accordingly, there is no motivation in either Cais or Neilson to combine the two references and a skilled worker would not combine this reference with that of Cais to arrive at the present invention. Applicants request that the rejection be withdrawn.

IV. Anbar:

The Examiner rejected claims 19 and 23-25 on the basis of obviousness with regard to Cais in view of Foster and Anbar et al. Anbar et al. discloses the use of I, Br, Cl, Se, Te, ¹⁴C and ³H. These elements are not transition elements, isotopes or ions as recited in Claims 1, 3, 29 and 30. Further, Anbar et al. describes the use of elements that form negatively charged ions and uses a negative ion mass spectrometer for the detection device. At column 3, lines 35-40 Anbar et al. states:

Examples of these isotopes, which are preferred, are the ones which are not subject to back-ground noise caused by other negative ions present in the specimen being analyzed. Preferred stable isotopes, as previously indicated, are exemplified by ¹²⁷I

and ^{129}I if necessary, ^{81}Br , ^{36}Cl , ^{74}Se , ^{79}Se , ^{120}Te , ^{133}Te , ^{14}C , as well as tritium.

In contrast, the present invention employs transition elements. The transition elements that are presently disclosed more readily form positively charged ions. Applicants have amended claims 1, 3 and 29 by inserting the term “positively charged”. The limitations of the amended claims are not found in Cais, Foster et al. and Anbar. Accordingly, Applicants request that the rejection be withdrawn.

V. Crooke:

The Examiner rejected claims 22 and 26-27 on the basis of obviousness with regard to Cais in view of Foster et al. and Crooke. The Examiner states that Crooke discloses the use of a “plurality” of tagged transition elements and biologically active materials.

Crooke describes a method of identifying biomolecular targets using mass-modifying tags. The method involves the ionization of the entire tagged biomolecule, which is then fragmented in sequential collisions to produce fragment ions. The fragment ion mass spectrum is queried to determine the mass of the tag and to identify the positioning of the tag on the original biomolecule. Tags of differing mass are used to allow multiple biomolecule detection provided that the fragmentation spectra of the biomolecules and their tags are distinguishable. An alternative method disclosed requires the measurement of the fragmentation mass spectra of the biomolecule and then the measurement of the fragmentation mass spectra of the tagged biomolecule. Comparison of the spectra provides information on the site of binding.

The method of Crooke teaches ionization of the entire tagged biomolecule and not just the tag element itself, as in the present application. Applicant's claimed invention is clearly distinguished from the method of Crooke because only the tag element is measured in the present method (not the tagged biomolecule). In the present invention the tagged biomolecule is completely disintegrated in the ICP source down to its elemental components (nitrogen, oxygen, carbon and so on). Elemental MS does not have any other identifiable feature apart from the tag elemental composition. Applicant has amended claims 1, 3 and 29 by inserting the term “positively charged transition element” after the phrase “detecting and measuring”.

Accordingly, Cais, Foster et al. and Crooke do not disclose all the claim limitations in amended claims 1, 3 and 29. Applicants request that the rejection be withdrawn.

VI. Mire-Sluis et al.

The Examiner rejected claim 28 on the basis of obviousness with regard to Cais in view of Foster and Mire-Sluis. Mire-Sluis disclose assays for cytokines. However, all the claim limitations of the amended claims are not found in the combination of Cais, Foster and Mire-Sluis as described above. Applicants request that the rejection be withdrawn.

In addition, Applicants submit herewith evidence under 37 C.F.R. § 1.132 of the non-obviousness of the invention, in the form of a Declaration by Scott D. Tanner, PhD. (Exhibit A), and supporting exhibits (Exhibits B to Y). Such evidence clearly establishes the non-obviousness of each of the claims presented in the application.

Graham Factors: Declaration of Scott D. Tanner

In further support of its arguments demonstrating that the invention as claimed is not obvious in light of the prior art, Applicant attaches the Declaration of Scott D. Tanner, PhD (hereinafter “the Declaration”). This Declaration was filed against the parent application (09/905,907). As noted in the Declaration, Dr. Tanner is a University professor having more than 29 years’ experience in the field of the invention (Para. 1 of the Declaration). Dr. Tanner states that:

- Inductively Coupled Plasma (ICP) mass spectrometry was first described more than 20 years prior to the filing of the application herein. (Para. 3 and Exhibit B.)
- The tagging of biologically active material dates at least to the introduction of radioactive tagging in 1948, more than 50 years prior to the filing of the application herein. (Para. 4 and Exhibit C.)
- The earliest specific reference to a highly-multiplexed method of detecting analytes of which Dr. Tanner is aware dates to 1977, more than 20 years prior to the filing of the application herein, while efforts to implement such a method have been sought continuously since. The need has been driven, for example, in applications such as the detection of markers on cancer cells, of toxins in environmental samples, of

endogenous proteins in cells, of exogenous proteins in cultured cells following transfection, of elemental species, of receptors in drug discovery assays, and of ischemic markers in patients believed to have suffered heart attack. (Para. 9 and Exhibit D.)

- The need for highly-multiplexed methods of detecting analytes has persisted, and if anything has grown more compelling over the years, driven, for example, by the ongoing discovery of numerous biological markers in cells, the increased use of transfection in biomedical research, the increased testing of environmental samples, and increased drug discovery research. (Para. 10.)
- In spite of the foregoing, no one thought of or succeeded in conceiving and reducing to practice the invention disclosed in the application herein until the inventors named herein, at the time of the filing of the application. (Para. 11.)
- Others have tried, but failed, to provide systems, methods, and apparatus capable of highly-multiplexed detection of analytes. For example, scientists have attempted to provide such capability through the use of fluorescent flow cytometry, microarrays, and "multi-coloured" beads. None of these attempted solutions has proved satisfactory. (Para. 12.)
- The invention disclosed and claimed in the application herein, and specific applications of the invention, have been praised as important and innovative steps by numerous respected and independent members of the scientific community, including the Scientific Review Committee of the Genome Canada Applied Health Grant Competition and the Grant Review Committee of the U.S. National Institute of Health, both of which reviewed grant applications for projects enabled by and otherwise related to the invention claimed herein. See, for example, Exhibits E and F attached to Dr. Tanner's Declaration, and specific comments cited therein. (Para. 13 and Exhibits E and F.)
- Since the first public disclosure of the invention claimed herein, the invention has attracted significant attention among independent and respected researchers, and has spawned a large amount of subsequent research. Since, for example, the first publication of descriptions of the invention by the inventors, the inventors' publications have been cited by at least 19 further papers, which 19 have been cited

by numerous additional researchers. See, for example, citation lists in and Exhibits K through Y attached to Dr. Tanner's declaration. (Para. 14, Exhibits H through Y.)

Each of the stated facts provides strong support for non-obviousness under the framework set forth by the United States Supreme Court decision in its decision in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966):

Under [35 USC] § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

The need to consider secondary factors such as long-felt but unsolved needs was clarified and emphasized by the Court of Appeals for the Federal Circuit in *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 USPQ2d 1434 (Fed. Cir. 1988):

Objective evidence of nonobviousness "must always when present be considered en route to a determination of obviousness" because: evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art.

and in *Iron Grip Barbell Co. v. USA Sports Inc.*, 73 USPQ2d 1225 (Fed. Cir. 2004):

This court has previously identified, *inter alia*, commercial success, satisfaction of a long-felt need, and copying to be relevant factors in this inquiry. See *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir.

1988) (commercial success); *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1054 (Fed. Cir. 1988) (long-felt need); *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1574 (Fed. Cir. 1996) (copying).

Dr. Tanner's testimony and the Exhibits attached to his declaration clearly demonstrate that the need for spectrographic analysis of analytes, including particularly multiplexed analysis, as recited by the claims, had been felt for at least 20 - 50 years prior to the filing of the application herein; and that others working in the field tried a number times, using various approaches and without success, to fill that need. Thus the invention has satisfied a long-felt need.

Moreover, Exhibits E and F attached to Dr. Tanner's declaration clearly demonstrate that the independent scientific community considers the claimed invention to be an important and highly innovative success, with almost certain imminent commercial success. Exhibits K through Y clearly demonstrate that the independent scientific community considers the claimed invention to be worthy of copying, both for purposes of immediate application and for use in extended research.

Applicant notes particularly the acknowledgment of Dr. Joanna Szpunar of the French National Research Council in Exhibit U:

The use of ICP MS in this context was pioneered by Baranov et al. who developed a very sensitive immunoassay using gold-tagged antibodies... It should be noted that a number of elemental tags for proteins and peptides exist but have never been used in combination with ICP MS.

Exhibit U at pg. 446, col. 2, lines 5 - 12, citing Applicant's publication in Exhibit H.

It is accordingly clear that the claims as presented would not have been obvious at the time the invention was made to a person having ordinary skill in the art, as specified by 35 USC § 103(a). Applicant respectfully requests reconsideration and withdrawal of the rejections, and allowance of the claims.

CONCLUSION

Applicant believes that the present application is now in condition for allowance.
Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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